AF/1600

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Mountz, et al.	§	**ART UNIT: 1647**
FILED: May 15, 1998	§	
SERIAL NO.: 09/079,834	§	**EXAMINER: Spector, Lorraine**
FOR: Fas Ligand Expressing Antigen Presenting Cells for Tolerance Induction	§	**DOCKET: D6005**

Mail Stop AF
Commissioner for Patents
P.O. BOX 1450
Alexandria, VA 22313

TRANSMITTAL OF APPEAL BRIEF

Dear Sir:

Enclosed please find three Originals of the Appeal Brief for the above-referenced patent application.

The Commissioner is hereby authorized to charge Deposit Account No. 07-1185 in the total amount of $160 for the appeal fee and any additional fee that may be required. Please credit any overpayment or debit any underpayment to Deposit Account 07-1185.

Respectfully submitted,

Date: Aug 28, 2003

ADLER & ASSOCIATES
8011 Candle Lane
Houston, Texas 77071
(713) 270-5391
BADLER1@houston.rr.com

Benjamin Aaron Adler, Ph.D., J.D.
Registration No. 35,423
Counsel for Applicant

CERTIFICATE OF MAILING UNDER 37 CFR 1.8

I hereby certify under 37 CFR 1.8 that the following correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to: MS AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313:

1) Three (3) copies of Appeal Brief.
2) Transmittal of Appeal Brief; and

Please return the enclosed postcard acknowledging receipt of this correspondence.

Respectfully submitted,

Date: Aug 28, 2003

Benjamin Aaron Adler, Ph.D., J.D.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Mountz, et al.	§	ART UNIT: 1647
FILED: May 15, 1998	§	
SERIAL NO.: 09/079,834	§	EXAMINER: Anne Marie Wehbe
FOR: Fas Ligand Expressing Antigen Presenting Cells for ToleranceInduction	§	DOCKET: D6005

Mail Stop Appeal Brief - Patents
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313

ATTENTION: Board of Patent Appeals and Interferences

APPELLANT'S BRIEF

This Brief is in response to Notification of Non-Compliance with 37 C.F.R. 1.192(c) mailed August 12, 2003.

In accordance with 37 C.F.R. §1.192(a), this Brief is submitted in triplicate.

INDEX OF SUBJECT MATTER

I. REAL PARTY IN INTEREST

The real party in interest is the University of Alabama at Birmingham Research Foundation.

II. STATUS OF THE CLAIMS

Originally claims 1-17 were filed with this Application. Claims 10-15 were withdrawn from consideration. Claims 2, 7 and 17 were canceled, and claims 1, and 16 have been amended. The pending claims 1, 3-6, 8, 9 and 16 are being appealed, of which claims 1 and 16 are independent claims.

III. STATUS OF AMENDMENTS

No claim amendment was made in response to the Final Office Action mailed September 3, 2002. All pending claims are shown in the Appendix.

IV. STATEMENT OF RELATED APPEALS AND INTERFERENCES

To Applicant's knowledge, there are no pending related appeals or interferences that will directly affect or be directly affected by the present appeal.

V. SUMMARY OF THE INVENTION

The present invention is drawn to a method of inducing systemic tolerance to a viral or alloantigen using antigen presenting cells engineered to express Fas ligand and the antigen of interest. These antigen presenting cells would induce apoptosis of Fas-positive T cells directed towards said antigen through the Fas ligand-Fas antigen interaction. Subsequently, systemic tolerance to said antigen is induced (Specification, page 9, line 3-page 10, line 5).

The present invention is also drawn to a method of using antigen presenting cells engineered to express Fas ligand to reduce graft rejection. Antigen presenting cells from a graft are engineered to express high level of Fas ligand. These antigen presenting cells would eliminate T cells reactive to the antigens of the graft as described above. As a result, immune-privileged sites are created in

which the graft is not rejected due to T cell tolerance. (Specification, page 24, line 19-page 25, line 10).

VI. ISSUES

35 U.S.C. §112

Whether claims 1, 3-6, 8, 9 and 16 are enabled under 35 U.S.C. §112, first paragraph.

VII. GROUPING OF CLAIMS

The rejected claims do not stand or fall together. Applicant considers claims 1, 3-6, 8, 9 and 16 encompass two embodiments of the present invention. Claims 1, 3-6 and 8-9 are drawn to a method of inducing systemic tolerance to a viral antigen, an autoantigen or an alloantigen using Fas ligand-expressing antigen presenting cells. In another embodiment, claim 16 is drawn to a method of creating immune-privileged sites so as to decrease transplant rejection.

VIII. ARGUMENTS

The Rejection Under 35 U.S.C. §112

In the Final Office Action mailed September 3, 2002, the Examiner maintained the rejection of claims 1, 3-6, 8, 9 and 16 under 35 U.S.C. §112, first paragraph, for lack of enablement. This rejection is respectfully traversed.

The present invention discloses a strategy in which introduction of antigen presenting cells (APCs) engineered to express high levels of Fas ligand together with a specific antigen could induce specific, systemic tolerance to the antigen. A series of experiments were performed to examine tolerance induction *in vivo* by these Fas ligand-expressing antigen presenting cells (Examples 17, 18, 20, 21 and Figures 7, 8, 10B and 11). It was shown that APCs, which expressed Fas ligand and processed adenovirus antigens, can directly induce apoptosis of Fas-positive T cells. Pretreatment of recipient mice with the adenovirus-transfected Fas ligand-expressing APCs resulted in induction of T cell tolerance to the adenovirus. Induction of T cell tolerance to adenovirus required production of Fas ligand by the APCs and did not occur with adenovirus-transfected, control APCs. T cell tolerance also required expression

of Fas by the T cells of recipient mice, as Fas-deficient lpr/lpr mice could not be tolerized. This is because T cell tolerance is a result of eliminating activated T cells by apoptosis which is induced upon binding the Fas antigens on the T cells to the Fas ligands expressed on the antigen presenting cells. The T cell tolerance was antigen-specific as there was normal T-cell response to murine cytomegalovirus (MCMV) in tolerized mice.

Applicant further submits data in a Declaration filed June 20, 2002, showing T cell tolerance induction by Fas ligand-expressing APCs in murine models of Sjögren syndrome–like disease and arthritis. Sjögren syndrome is a chronic inflammatory disease characterized by infiltration of the exocrine glands with mononuclear cells and T cells. Induction of T cell tolerance resulted in dramatic amelioration of these diseases in the infected animals. Hence, Applicant submits that ample data have been provided to show T cell tolerance induction by Fas ligand-expressing antigen presenting cells in not one but multiple well-recognized disease models in the art. In view of these results, Applicant submits that one of ordinary skill in the art would find it convincing to correlate and extrapolate the animal data to applications in human.

The Examiner rejects the instant invention based on the assumption that the claimed methods are methods of gene therapy. Attempting to show a potential problem in applying the instant invention to human, the Examiner made reference to the death of a patient in a gene therapy trial in the Final Office Action mailed March 23, 2001. Applicant submits, however, the present invention is not gene therapy and the purported problems associated with gene therapy are not issues in the instant invention.

Gene therapy protocols generally involve administering to a patient retroviral or adenoviral vectors that carry the desirable genetic material. A number of technical problems, as well as the death of a patient cited above, are associated with the use of these viral vectors. The present invention, however, does not involve or require administration of viral vectors to a patient. The present invention only requires administering to an individual genetically modified antigen presenting cells, and transfusing such cells to an individual would not cause any potential problems associated with gene therapy.

The present invention is designed to down-regulate immune responses by the expression and function of Fas ligand. In normal situation, naïve T cells become activated after interacting

with antigen presenting cells that process and present antigens to the T cells. The activated T cells are then capable of mediating a number of immune functions. These activated T cells also express Fas antigens on their surface. In the present invention, these activated T cells would be eliminated by apoptosis which is induced upon binding the Fas antigens on the T cells to the Fas ligands expressed on the antigen presenting cells. Consequently, T cell tolerance is induced and the individual would have significantly reduced immune responses towards the antigens presented by the Fas ligand-expressing antigen presenting cells.

In order to practice the instant invention, one of ordinary skill in the art only need to generate by routine and standard molecular biology techniques engineered antigen presenting cells that express an antigen of interest and Fas ligand. After being introduced to an individual by standard procedure, these antigen presenting cells would engage and present antigens to naïve T cells just like normal unmodified antigen presenting cells. Consequently, activated T cells that are reactive to the antigens presented by these modified antigen presenting cells would be eliminated by apoptosis as described above.

The method of claim 1 requires antigen presenting cells that express the antigen of interest. This antigen can be naturally occurring in these cells or expressed in these antigen presenting cells by genetic engineering. These antigen presenting cells are further co-infected with AdLoxPFasL and AxCANCre adenoviruses to express high level of Fas ligand before transfused into an individual. Applicant submits that these steps of cell preparation and genetic engineering can be readily performed by one of ordinary skill in the art, and no undue experimentation is required in the making, administering and using of the engineered antigen presenting cells as claimed in claim 1.

In another embodiment of the present invention, claim 16 provides a method of decreasing rejection of a tissue graft. Applicant submits that the methods of claim 16 and that of claim 1 are separately patentable. Initially, Applicants note that the antigen presenting cells (APCs) used in the method of claim 1 are self antigen presenting cells, i.e., antigen presenting cells derived from the individual undergoing treatment, whereas the antigen presenting cells used in the method of claim 16 are foreign antigen presenting cells, i.e., antigen presenting cells extracted from donor organ tissue. These foreign antigen presenting cells are infected with

AdLoxPFasL and AxCANCre adenoviruses to produce Fas ligand-expressing antigen presenting cells which are then introduced into an individual prior to and during the grafting procedure. In contrast, the method of claim 1 does not require multiple administration of antigen presenting cells as recited in claim 16. Thus, the methods of claim 16 and that of claim 1 differ in the source of antigen presenting cells and the frequency of administrating the modified antigen presenting cells to an individual.

Applicant submits that the method steps recited in claim 16 can be readily performed by one of ordinary skill in the art. Extracting antigen presenting cells from donor organ, infecting the isolated antigen presenting cells with adenoviral vectors and then transferring the modified antigen presenting cells into an individual can all be performed according to standard and well-known procedures in the art. Moreover, one of skill in the art would have reasonable expectation of success in inducing tolerance and decreasing graft rejection in view of the *in vivo* results presented in the present application.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the

patent coupled with information known in the art without undue experimentation (M.P.E.P. §2164.01). Based on the data disclosed herein, Applicant submits that detailed description of *in vivo* effects of Fas ligand-expressing antigen presenting cells disclosed in the specification has provided sufficient enablement for using said antigen presenting cells to induce T cell tolerance in human. The scope of the claims is commensurate with the enablement provided. Accordingly, Applicant respectfully requests that the rejection of claims 1, 3-6, 8, 9 and 16 under 35 U.S.C. §112, first paragraph, be reversed.

Respectfully submitted,

Date: Aug 28, 2003

Benjamin Aaron Adler, Ph.D., J.D.
Registration No. 35,423
Counsel for Applicant

ADLER & ASSOCIATES
8011 Candle Lane
Houston, Texas 77071
(713) 270-5391 (tel.)
(713) 270-5361 (facs.)
badler1@houston.rr.com

CLAIMS ON APPEAL

1. (twice amended) A method of inducing systemic tolerance to an antigen in an individual in need of such treatment, comprising the step of:

administering to said individual antigen presenting cells which (1) express high level of Fas ligand resulted from co-infection with AdLoxPFasL and AxCANCre adenoviruses, (2) do not express Fas and (3) express said antigen, wherein said antigen presenting cells induce apoptosis of Fas-positive T-cells directed towards said antigen resulting in said induction of systemic tolerance to said antigen.

3. The method of claim 1, wherein said antigen is selected from the group consisting of the adenovirus antigen, a viral antigen, an adeno-associated viral antigen, an autoantigen, and an alloantigen.

4. The method of claim 1, wherein said individual has an autoimmune disease.

5. The method of claim 4, wherein said autoimmune disease is selected from the group consisting of diabetes, multiple sclerosis, rheumatoid arthritis, thyroiditis, Grave's disease, systemic lupus erythematosus.

6. The method of claim 1, wherein said individual has had an organ transplant.

8. The method of claim 1, further comprising the step of delivering to said antigen presenting cells a gene to inhibit apoptosis.

9. The method of claim 8, wherein said gene to inhibit apoptosis is crmA.

16. (twice amended) A method of creating immune-privileged sites in an individual so as to decrease rejection of a graft, comprising the steps of:

extracting antigen presenting cells from donor organ tissue;

introducing Fas ligand into said antigen presenting cells by co-infection with AdLoxPFasL and AxCANCre adenoviruses to produce Fas ligand-expressing antigen presenting cells expressing an antigen specific to said graft;

introducing said Fas ligand-expressing antigen presenting cells expressing an antigen specific to said graft to said individual prior to and during said grafting procedure; wherein said Fas ligand-expressing antigen presenting cells expressing an antigen specific to said graft create said immune-privileged site at the site of said grafting procedure to prevent rejection of said graft in said individual.